REMARKS

Claims 18-50 were pending in this application. In order to expedite prosecution and without conceding to the validity of the rejections, Applicants have canceled claims 20, 23 and 28-31, without prejudice to Applicants' right to pursue the subject matter of the canceled claims in one or more related applications. Applicants have amended claims 39-44, 48 and 49 to delete their dependency from one or more of the canceled claims. Applicants have amended claims 18, 19, 21, 22, 32, 41, 43 and 46-50 and added new claims 51-62 to more particularly point out and distinctly claim that which Applicants regard as their invention.

Applicants have amended claims 18, 19, 21, 22 and 32 to recite that the subject animals are in need of inhibiting or suppressing viral or microbial replication or treatment for septic shock. Applicants have amended independent claim 32 to recite that the animal is administered a therapeutically effective amount of one or more anti-C3b(i) antibodies to treat septic shock. Dependent claims 41 and 43 have been amended to clarify that the anti-C3b(i) antibody is immunospecific for C3b(i) linked to an IgM antibody or an IgG antibody, which IgM antibody or IgG antibody is bound to a virus or a microbe, respectively. Dependent claims 48 and 50 have been amended to correct typographical errors and the antecedent basis for the claims. Further, dependent claims 46, 47 and 49 have been amended to correct the antecedent basis for the claims.

New independent claim 51 (and claims dependent therefrom) recites a method for inhibiting or suppressing viral replication in an animal, comprising administering to the animal a therapeutically effective amount of is a bispecific antibody which is immunospecific for (i) C3b(i) and (ii) an effector cell receptor or antigen. Dependent claims 52 and 53 specify the effector cell or antigen other than C3b(i) to which the bispecific antibody immunospecifically binds. Dependent claims 54-56 recite that IgG enriched plasma, IgM enriched plasma or one or more complement components, respectively, are administered to the animal in combination with the bispecific antibody recited in claim 51. Dependent claims 57 and 58 specify that the animal receiving the bispecific antibody is a mammal and a human, respectively. Dependent claims 59 and 60 further specify the specificity of the bispecific antibody. Dependent claim 61 specifies the virus whose replication is being inhibited or suppressed by administration of the bispecific antibody. Dependent claim 62 recites that the antibody is specific for the C3b(i) fragment

The amendments to the claims are fully supported by the specification of the present application, see, *e.g.*, page 5, line 24 to page 6, line 5, page 7, lines 6-7, page 10, line 9 to

page 11, line 22, page 13, line 4 to page 14, line 9, page 15, line 1 to page 17, line 14, page 21, line 19 to page 26, line 24, page 27, line 28 to page 28, line 17, page 34, line 8 to page 35, line 36, and page 40, line 4 to page 43, line 7 and do not constitute new matter. Upon entry of this Amendment, claims 18, 19, 21, 22, 24-27 and 32-62 will be pending in the present application.

Entry of the foregoing amendments and consideration of these remarks are respectfully requested.

1. THE OBJECTIONS TO THE CLAIMS SHOULD BE WITHDRAWN

Claims 48 and 50 are objected to because of the following informalities: (a) "claim 50 consists of more than one sentence and repeats species of the first sentence within the second sentence"; (b) "claim 50, line 8 has a typographical error in the spelling of '*pseudotuberculosis*'"; and (c) "claim 48 has a typographical error in the spelling of 'coronavirus'". In response, Applicants have amended claims 48 and 50, respectively, to correct the typographical errors in the spelling of "coronavirus" and "*pseudotuberculosis*", and have deleted the second sentence in claim 50. Applicants also recognized that orthomyxovirus was likewise misspelled and have corrected it as well. Thus, the objections to claims 48 and 50 are moot. Accordingly, Applicants respectfully request withdrawal of the objections.

2. THE REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH, SHOULD BE WITHDRAWN

Claim 41 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. In particular, the Examiner contends that it is unclear if IgM is required to be bound to a virus. For the reasons below, the rejection cannot stand and should be withdrawn.

In reviewing a claim for compliance for 35 U.S.C. § 112, second paragraph, the Examiner must analyze the claim in view of the specification, the prior art, and the interpretation that would be given by one of ordinary skill in the relevant art. M.P.E.P. § 2173.02 (Eighth edition, Revision 2, May 2004).

Applicants respectfully assert that one of ordinary of skill in the art would understand that the anti-C3b(i) antibody is immunospecific for: (i) C3b(i) linked to an IgM antibody

which IgM antibody is bound to virus; or (ii) C3b(i) linked to an IgG antibody which IgG antibody is bound to virus. However, in order to expedite the prosecution of the application and without conceding to the propriety of the rejection, Applicants have amended claim 41 to recite that the anti-C3b(i) is immunospecific for C3b(i) linked to an IgM antibody or an IgG antibody, which IgM antibody or IgG antibody is bound to a virus. Thus, the rejection of claim 41 under 35 U.S.C. § 112, second paragraph, cannot stand and should be withdrawn.

3. THE REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, SHOULD BE WITHDRAWN

Claims 20, 23, 28-31, 39-44 and 46-50 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. Claims 20, 23, 28-31, 39-44 and 46-50 are also rejected under 35 U.S.C. § 112, first paragraph, for lack of written description.

Without acquiescing to the propriety of the rejections, Applicants point out that claims 20, 23 and 28-31 have been canceled, without prejudice, and claims 39-44, 48 and 49 have been amended to delete their dependency on canceled claims 20, 23 and/or 28-31. Thus, the rejections of claims 20, 23, 28-31, 39-44 and 46-50 under 35 U.S.C. § 112, first paragraph, are moot and cannot stand. Accordingly, Applicants respectfully request withdrawal of the rejection.

4. THE CLAIMED INVENTION IS NOT OBVIOUS

4.1 Taylor In View of Stoiber Does Not Render Claims 18, 19, 38, 39, 40, 42, 46 and 48 Obvious

Claims 18, 19, 38, 39, 40, 42, 46 and 48 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Taylor et al., U.S. Patent No. 5,470,570 (hereinafter "Taylor") in view of the abstract of Stoiber et al., 1995, Immunobiology 193: 98-113 (hereinafter "Stoiber"). The Examiner contends that: (1) Taylor teaches "a method of using franked red blood cells with specificity to an antigen such as HIV to clear free antigen from the blood of a human patient ... and a method of using franked red blood cells with specificity to C3b"; and (2) Stoiber "teaches that C3b reacts with the gp120 envelope protein of HIV-1." The Examiner contends that "[i]t would have been prima facie obvious to one of skill in the art at the time the invention was made to frank red blood cells with a cocktail of heteropolymers which comprised of anti-CR1 antibodies which bound to different epitopes of CR1,

conjugated to anti-C3b antibodies, and anti-C3b antibodies which bind to C3b attached to gp120 and to administer said franked red blood cells for the treatment of HIV infection ...." The Examiner contends that one of skill in the art would have been motivated to administer such franked red blood cells because of the teaching in Stoiber regarding the deposition of C3b on HIV-1 and the specific interaction of C3b with gp120. For the reasons detailed below, the rejection cannot stand and should be withdrawn.

A finding of obviousness requires a determination of the scope and content of the prior art, the level of ordinary skill in the art, the differences between the claimed subject matter and the prior art, and whether the differences are such that the subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. *Graham v. Deere* 383 U.S. 1 (1996). The proper inquiry is whether the art suggests the invention, and whether the art provides one of ordinary skill in the art with a reasonable expectation of success. *In re O'Farrell* 853 F.2d 894, 7 USPQ2d 1673 (Fed. Cir. 1988). Both the suggestion and the reasonable expectation of success must be founded in the prior art and not in the Applicants' disclosure. *In re Vaeck* 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). It is impermissible to engage in hindsight reasoning, using the claims as a frame and the prior art reference as a mosaic to piece together a facsimile of the claimed invention. *W.L. Gore & Assoc., Inc. v. Garlock, Inc.* 220 USPQ 303, 312 (Fed. Cir. 1983).

Neither Taylor nor Stoiber, alone or in combination, teach or suggest the methods recited in the pending claims. Taylor teaches heteropolymers comprising a monoclonal antibody specific to the erythrocyte complement receptor protein CR1 chemically bound to a monoclonal antibody specific to at least one other antigen, and the use of such heteropolymers to produce "franked" erythrocytes (*i.e.*, erythrocytes bound to the heteropolymers) for neutralizing and/or clearing antigens or immunogens from the circulatory system (see the abstract of Taylor). Taylor teaches administering heteropolymers directly into the bloodstream or extracting erythrocytes from a patient, binding the erythrocytes with the heteropolymers and administering the franked erythrocytes to the patient to facilitate neutralization and/or clearance of antigens or immunogens from the circulatory system (see the abstract and column 7, lines 16-24 of Taylor).

Taylor does not teach, suggest or contemplate methods of inhibiting or suppressing viral replication in an animal comprising administering to the animal an anti-C3b(i) antibody, much less a bispecific antibody immunospecific for: (i) C3b(i) and (ii) an effector cell receptor or antigen. As acknowledged by the Examiner on page 12, sixth full paragraph of the Office Action mailed March 15, 2005, "neither Taylor ... nor ... Stoiber ... teach bi-

specific antibodies which bind CR1 and C3b." Although Taylor mentions the term "C3b" once in the specification, it is unclear in the context of the paragraph what heteropolymer Taylor is contemplating using to produce franked erythrocytes and use of such franked erthrocytes. See Taylor at column 6, line 67 to column 7, line 10 which teaches that the most important therapeutic uses for franked erthyrocytes include:

> (1) using franked RBC of the invention with specificity to an antigen such as HIV to clear free antigen from the blood of a human or primate patient, (2) using a franked erthrocyte with a Mab specific for a non-immunogenic but potentially "pathogenic" target such as LDL which has been linked to atherosclerosis and (3) using a franked erythrocyte with Mab specificity for the natural ligand of CR1 (such as C3b) where the number of naturally occurring receptors in an individual patient has decreased, such as in systemic lupus erythematosus.

Thus, Taylor does not teach, suggest or contemplate methods of inhibiting or suppressing viral replication in an animal comprising administering: (i) erythrocytes franked by a heteropolymer comprising a monoclonal antibody specific to CR1 chemically bound to a monoclonal antibody specific to C3b(i); or (ii) heteropolymers comprising a monoclonal antibody specific to CR1 chemically bound to a monoclonal antibody specific to C3b(i). Taylor merely teaches using franked erythrocytes with specificity for a ligand of CR1 in patients with, for example, lupus.

Further, Taylor does not teach, suggest or contemplate methods of inhibiting or suppressing viral replication in an animal comprising administering to the animal an anti-C3b(i) antibody and an antibody immunospecific for one or more viral antigens. As discussed above, Taylor teaches the using heteropolymers to neutralize and/or clear antigens or immunogens from the circulatory system, which heteropolymers comprise a monoclonal antibody specific to CR1 chemically bound to a monoclonal antibody specific to at least one other antigen. Taylor does not teach or suggest administering to an animal a heteropolymer comprising a monoclonal antibody specific to C3b(i) chemically bound to a monoclonal antibody specific for a viral antigen, much less administering to an animal an anti-C3b(i) antibody and an antibody immunospecific for a viral antigen.

The deficiencies of Taylor are not cured by Stoiber. Stoiber describes the interaction of HIV-1 gp120 with human C3b and HIV-1 gp41 with human factor H and properdin. Stoiber does not teach, suggest or contemplate methods of inhibiting or suppressing viral replication in an animal comprising administering to the animal an anti-C3b(i) antibody,

whether a monoclonal antibody immunospecific for C3b(i) or a bispecific antibody immunospecific for C3b(i) and an effector cell or antigen. Further, Stoiber does not teach, suggest or contemplate methods of inhibiting or suppressing viral replication in an animal comprising administering to the animal an anti-C3b(i) antibody and an antibody immunospecific for one or more viral antigens. Moreover, one of skill in the art would not have been motivated to administer franked red blood cells or a heteropolymer comprising a monoclonal antibody specific for CR1 chemically bound to a monoclonal antibody specific for C3b(i) for treatment of viral or microbial infection or septic shock because of the suggestion in the full-length article of Stoiber (a copy of which is included with the Supplemental Information Disclosure Statement submitted herewith) that the interaction of HIV-1 gp120 with complement proteins, such as C3b, makes a CD4-independent infection of cells via complement receptors, such as CR1, seem possible (see Stoiber at page 110, last paragraph), i.e., the method could increase, not ameliorate HIV infection. Thus, Stoiber, rather than suggesting the claimed invention, actually teaches away from it.

In view of the foregoing, the rejection of claims 18, 19, 38, 39, 40, 42, 46 and 48 under 35 U.S.C. § 103(a) as being unpatentable over Taylor in view of Stoiber cannot stand and should be withdrawn.

4.2 Taylor In View Stoiber and Nilsson Does Not Render Claims 18, 19, 34, 38, 39, 40-42, 46 and 48 Obvious

Claims 18, 19, 34, 38, 39, 40-42, 46 and 48 are rejected under 35 U.S.C. § 103(a) as unpatentable over Taylor and Stoiber as applied to claims 18, 19, 38, 39, 40, 42, 46, and 48, and further in view of Nilsson et al., 1987, Molecular Immunology 24: 487-494 (hereinafter "Nilsson"). For the reasons recited in Section 4.1 above, the Examiner contends that Taylor and Stoiber render obvious claims 18, 19, 38, 39, 40, 42, 46, and 48. The Examiner contends that Nilsson teaches "monoclonal anti-C3d antibodies which bind exclusively to neoantigenic epitopes found in physiologically bound C3". The Examiner contends that "[i]t would have been prima facie obvious to one of skill in the art at the time the invention was made to use the monoclonal antibody anti-C3(d) antibodies as taught by Neilsson [sp] ... as part of the heteropolymer rendered obvious by the combination of Taylor ... and ... Stoiber ...." The Examiner contends that one of skill in the art would have been motivated to use such monoclonal antibodies because of the teaching in Nilsson regarding the ability of the anti-

C3d antibodies to bind to physiologically bound forms of C3. For the reasons detailed below, the rejection cannot stand and should be withdrawn.

As discussed above in Section 4.1, neither Taylor nor Stoiber, alone or in combination, teach or suggest the methods of independent claims 18 and 19 (and claims dependent therefrom, including claims 38, 39, 40, 42, 46, and 48) and new independent claim 51 (and claims dependent therefrom).

Nilsson does not cure the deficiencies of Taylor and Stoiber. Nilsson describes the production of murine monoclonal antibodies that bind to distinct neoantigenic epitopes on bound C3b and C3b(i). Nilsson does not teach, suggest or contemplate methods of inhibiting or suppressing viral replication in an animal comprising administering to the animal an anti-C3b(i) antibody, whether a monoclonal antibody immunospecific for C3b(i) or a bispecific antibody immunospecific for C3b(i) and an effector cell or antigen. Further, Nilsson does not teach, suggest or contemplate methods of inhibiting or suppressing viral replication in an animal comprising administering to the animal an anti-C3b(i) antibody and an antibody immunospecific for one or more viral antigens, as recited in pending independent claim 19. Accordingly, the rejection of claims 18, 19, 34, 38, 39, 40-42, 46 and 48 under 35 U.S.C. § 103(a) as unpatentable over Taylor and Stoiber as applied to claims 18, 19, 38, 39, 40, 42, 46, and 48, and further in view of Nilsson cannot stand and should be withdrawn.

4.3 Taylor In View of Stoiber, Nilsson and Queen Does Not Render Claims 18, 19, 34, 35, 38, 39, 40-42, 46 and 48 Obvious

Claims 18, 19, 34, 35, 38, 39, 40-42, 46 and 48 are rejected under 35 U.S.C. § 103(a) as unpatentable over Taylor, Stoiber and Nilsson as applied to claims 18, 19, 34, 38, 39, 40-42, 46, and 48, and further in view of Queen et al., U.S. Patent No. 5,530,101 (hereinafter "Queen"). For the reasons recited in Sections 4.1 and 4.2 above, the Examiner contends that Taylor, Stoiber and Nilsson render obvious claims 18, 19, 34, 38, 39, 40-42, 46, and 48. The Examiner also contends that: (i) Taylor teaches "that human monoclonal antibodies can be used to prepare the heteropolymers to avoid [any] host immune response"; and (ii) Queen teaches "that the immune response mounted by a patient against a non-human antibody can be quite strong, essentially eliminating the therapeutic effect of the antibody ...", and provides methods for making humanized antibodies. The Examiner contends that "[i]t would have been prima facie obvious to one of skill in the art at the time the invention was made to

make the heteropolymer rendered obvious by the combination of Taylor ... and ... Stoiber ... with a humanized anti-C3(D) antibody as taught by Nilsson ...." The Examiner contends that one of skill in the art would have been motivated to make such a heteropolymer because of the suggestion in Taylor that human antibodies be utilized in the heteropolymer and the teachings of Queen regarding humanized antibodies. For the reasons detailed below, the rejection cannot stand and should be withdrawn.

As discussed above in Sections 4.1 and 4.2, neither Taylor, Stoiber nor Nilsson, alone or in combination, teach or suggest the methods of independent claims 18 and 19 (and claims dependent therefrom, including claims 34, 38, 39, 40-42, 46, and 48) and new independent claim 51 (and claims dependent therefrom).

The deficiencies of Taylor, Stoiber and Nilsson are not cured by Queen. Queen describes methods for producing humanized antibodies, and compositions comprising such humanized antibodies. Queen does not teach, suggest or contemplate methods of inhibiting or suppressing viral replication in an animal comprising administering to the animal an anti-C3b(i) antibody, whether a human or humanized monoclonal antibody immunospecific for C3b(i), or a bispecific antibody immunospecific for C3b(i) and an effector cell or antigen. Further, Queen does not teach, suggest or contemplate methods of inhibiting or suppressing viral replication in an animal comprising administering to the animal an anti-C3b(i) antibody and an antibody immunospecific for one or more viral antigens, much less such methods using a human or humanized anti-C3b(i) antibody and an antibody immunospecific for one or more viral antigens. Accordingly, the rejection of claims 18, 19, 34, 35, 38, 39, 40-42, 46 and 48 under 35 U.S.C. § 103(a) as unpatentable over Taylor, Stoiber and Nilsson as applied to claims 18, 19, 34, 38, 39, 40-42, 46, and 48, and further in view of Queen cannot stand and should be withdrawn.

4.4 Taylor In View of Stoiber, and Montefiori Does Not Render Claims 18, 19, 24-26, 34, 38, 39, 40, 42, 46 and 48 Obvious

Claims 18, 19, 24-26, 34, 38, 39, 40, 42, 46 and 48 are rejected under 35 U.S.C. § 103(a) as unpatentable over Taylor and Stoiber as applied to claims 18, 19, 38, 39, 40, 42, 46 and 48, and further in view of Montefiori et al., 1994, Journal of Infectious Diseases 170: 429-432 (hereinafter "Montefiori"). For the reasons recited in Section 4.1 above, the Examiner contends that Taylor and Stoiber render obvious claims 18, 19, 38, 39, 40, 42, 46, and 48. The Examiner contends that Montefiori teaches "that complement alone targeted

HIV-1 to red blood cells but that envelope-specific antibodies increased this effect", and "that the envelope-specific antibodies were obtained from gp-120-vaccinated volunteers." The Examiner contends that "[i]t would have been prima facie obvious to one of skill in the art at the time the invention was made to administer envelope-specific antibodies in addition to the franked erythrocytes rendered obvious by the combination of Taylor ... and ... Stoiber ...." The Examiner contends that one of skill in the art would have been motivated to administer such envelope-specific antibodies because of the teaching in Montefiori regarding the increase in binding to CR1 receptor by opsonized envelope-specific antibodies and complement. For the reasons detailed below, the rejection cannot stand and should be withdrawn.

As discussed above in Section 4.1, neither Taylor nor Stoiber, alone or in combination, teach or suggest the methods of independent claims 18 and 19 (and claims dependent therefrom, including claims 38, 39, 40, 42, 46, and 48) and new independent claim 51 (and claims dependent therefrom).

Montefiori does not cure the deficiencies of Taylor and Stoiber. Montefiori describes the effect of the addition of sera from infected or gp-160 vaccinated persons on the formation of HIV-1 immune complexes. Montefiori does not teach, suggest or contemplate methods of inhibiting or suppressing viral replication in an animal comprising administering to the animal an anti-C3b(i) antibody, whether a monoclonal antibody immunospecific for C3b(i) or a bispecific antibody immunospecific for C3b(i) and an effector cell or antigen, alone or in combination with the administration IgG or IgM enriched plasma. Further, Montefiori does not teach, suggest or contemplate methods of inhibiting or suppressing viral replication in an animal comprising administering to the animal an anti-C3b(i) antibody and an antibody immunospecific for one or more viral antigens, alone or in combination with the administration IgG or IgM enriched plasma. Moreover, one of skill in the art would not have been motivated to administer franked red bloods cells or a heteropolymer comprising a monoclonal antibody specific for CR1 chemically bound to a monoclonal antibody specific for C3b(i) and IgG or IgM enriched plasma because of the suggestion in Montefiori that "antibodies that promote HIV-1 immune complex formation could contribute HIV-1 pathogenesis by facilitating virus entry into CR-1 positive cells" (see Montefiori at page 432, last paragraph). Accordingly, the rejection of claims 18, 19, 24-26, 34, 35, 38, 39, 40, 42, 46 and 48 under 35 U.S.C. § 103(a) as unpatentable over Taylor and Stoiber as applied to claims 18, 19, 38, 39, 40, 42, 46 and 48, and in further view of Montefiori cannot stand and should be withdrawn.

4.5 Taylor In View of Stoiber, and Peng Does Not Render Claims 18, 19, 34, 38, 39, 40, 42, 46 and 48 Obvious

Claims 18, 19, 34, 38, 39, 40, 42, 46 and 48 are rejected under 35 U.S.C. § 103(a) as unpatentable over Taylor and Stoiber as applied to claims 18, 19, 38, 39, 40, 42, 46 and 48, and in further view of Peng et al., Clinical and Diagnostic Laboratory Immunology 3: 128-131 (hereinafter "Peng"). For the reasons recited in Section 4.1 above, the Examiner contends that Taylor and Stoiber render obvious claims 18, 19, 38, 39, 40, 42, 46, and 48. The Examiner concedes that these references do not teach the administration of one or more complement components. However, the Examiner contends that Peng teaches "that HIV-1 infection leads to complement deficient immune complexes." The Examiner contends that "[i]t would have been prima facie obvious to one of skill in the art at the time the invention was made to administer complement components in conjunction with the franked red blood cells rendered obvious by the combination of Taylor ... and ... Stoiber ..." The Examiner contends that "[o]ne of skill in the art would have been motivated to administer complement components in order to provide adequate C3b deposition on free HIV-1, so that the heteropolymers comprising the anti-C3bi antibodies on the franked red blood cells will bind multiple HIV viruses." For the reasons detailed below, the rejection cannot stand and should be withdrawn.

As discussed above in Section 4.1, neither Taylor nor Stoiber, alone or in combination, teach or suggest the methods of independent claims 18 and 19 (and claims dependent therefrom, including claims 38, 39, 40, 42, 46, and 48) and new independent claim 51 (and claims dependent therefrom).

The deficiencies in Taylor and Stoiber are not cured by Peng. Peng describes an increase in the amount of complement-deficient immune complexes following infection with HIV-1. Peng does not teach, suggest or contemplate methods of inhibiting or suppressing viral replication in an animal comprising administering to the animal an anti-C3b(i) antibody, whether a monoclonal antibody immunospecific for C3b(i) or a bispecific antibody immunospecific for C3b(i) and an effector cell or antigen, alone or in combination with the administration one or more complement components. Further, Peng does not teach, suggest or contemplate methods of inhibiting or suppressing viral replication in an animal comprising administering to the animal an anti-C3b(i) antibody and an antibody immunospecific for one

or more viral antigens, alone or in combination with the administration one or more complement components. Moreover, contrary to the Examiner's contention, one of skill in the art would not have been motivated to administer one or more complement components in conjunction with franked red blood cells or a heteropolymer comprising a monoclonal antibody specific for CR1 chemically bound to a monoclonal antibody specific for C3b(i) because Peng teaches that HIV-1 infected individuals have normal to elevated synthesis of complement factors and that the immune complexes in the infected individuals have immune complexes that are of a complement-poor subtype (see Peng at page 130 second full paragraph). Thus, the increase in the amount of complement-deficient immune complexes following HIV-1 infection does not seem to be the result of a lack of complement factors. Accordingly, the rejection of claims 18, 19, 34, 38, 39, 40, 42, 46 and 48 under 35 U.S.C. § 103(a) as unpatentable over Taylor and Stoiber as applied to claims 18, 19, 38, 39, 40, 42, 46 and 48, and in further view of Peng cannot stand and should be withdrawn.

4.6 Taylor In View of Stoiber, and Lenz Does Not Render Claims 18, 19, 33, 36-39, 40, 42, 46 and 48 Obvious

Claims 18, 19, 33, 36-39, 40, 42, 46 and 48 are rejected under 35 U.S.C. § 103(a) as unpatentable over Taylor and Stoiber as applied to claims 18, 19, 38, 39, 40, 42, 46 and 48, and in further view of Lenz et al., U.S. Patent No. 6,060,285 (hereinafter "Lenz"). For the reasons recited in Section 4.1 above, the Examiner contends that Taylor and Stoiber render obvious claims 18, 19, 38, 39, 40, 42, 46, and 48. The Examiner concedes that these references do not teach bispecific antibodies which bind CR1 and C3b. However, the Examiner contends that Lenz teaches "bispecific antibodies which have two different antigen binding sites directed towards two different epitopes useful for the therapy of diseases", and provides as an example of a bispecific antibody one which has one antigen binding site directed towards a T-cell surface antigen and a second antigen binding site directed towards an antigenic determinant of a virus. The Examiner contends that "[i]t would have been prima facie obvious to one of skill in the art at the time the invention was made to substitute bis-pecific antibodies which bind to both the CR1 receptor of a red blood cell and C3b on the target HIV-1 viron [sp] in the method rendered obvious by the combination of Taylor ... and ... Stoiber ..." The Examiner contends that one of skill in the art would have been motivated to make such a substitution because of the teaching in Lenz regarding the ease of making

bispecific antibodies relative to chemically conjugating two different antibodies and the high yield of bispecific antibodies obtained using the method in Lenz. For the reasons detailed below, the rejection cannot stand and should be withdrawn.

As discussed above in Section 4.1, neither Taylor nor Stoiber, alone or in combination, teach or suggest the methods of independent claims 18 and 19 (and claims dependent therefrom, including claims 38, 39, 40, 42, 46, and 48) and new independent claim 51 (and claims dependent therefrom).

Lenz does not cure the deficiencies of Taylor and Stoiber. Lenz describes methods for producing hetero-bispecific antibodies. Lenz does not teach, suggest or contemplate methods of inhibiting or suppressing viral replication in an animal comprising administering to the animal an anti-C3b(i) antibody, whether a monoclonal antibody immunospecific for C3b(i) or a bispecific antibody immunospecific for C3b(i) and an effector cell or antigen. Further, Lenz does not teach, suggest or contemplate methods of inhibiting or suppressing viral replication in an animal comprising administering to the animal an anti-C3b(i) antibody and an antibody immunospecific for one or more viral antigens. Accordingly, the rejection of claims 18, 19, 33, 36-39, 40, 42, 46 and 48 under 35 U.S.C. § 103(a) as unpatentable over Taylor and Stoiber as applied to claims 18, 19, 38, 39, 40, 42, 46 and 48, and in further view of Lenz cannot stand and should be withdrawn.

4.7 Taylor In View of Ebenbichler, and Nilsson Does Not Render Claims 18, 24, 34, 38, 39, 40 and 48 Obvious

Claims 18, 24, 34, 38, 39, 40 and 48 are rejected under 35 U.S.C. § 103(a) as unpatentable over Taylor in view of Ebenbichler et al., 1991, J. Exp. Med. 174: 1417-1424 (hereinafter "Ebenbichler") and Nilsson. The Examine contends that: (1) Taylor teaches "a method of using franked red blood cells with specificity to an antigen such as HIV to clear free antigen from the blood of a human patient ... and a method of using franked red blood cells with specificity to C3b"; (2) Ebenbichler teaches "that retroviruses isolated from avian, feline, murine and simian sources direct the induction of the classical complement pathway, whereas cells infected with retroviruses activate the alternative pathway"; and (3) Nilsson teaches "monoclonal anti-C3d antibodies which bind exclusively to neoantigenic epitopes found in physiologically bound C3". The Examiner contends that "[i]t would have been prima facie obvious to one of skill in the art at the time the invention was made to frank red

blood cells with a cocktail of heteropolymers which comprised of anti-CR1 antibodies which bound to different epitopes of CR1, wherein said anti-CR1 antibodies are conjugated to the anti-C3(D) antibody taught by Neilsson [sp] ... and to administer said franked red blood cells for the treatment of retrovirus infections." The Examiner contends that one of skill in the art would have been motivated to administer such franked red blood cells because of the teaching in Ebenbichler regarding the activation of complement by both free retroviruses and retrovirus-infected cells and the deposition of C3 onto retrovirus infected cells. For the reasons detailed below, the rejection cannot stand and should be withdrawn.

As discussed above in Section 4.1, Taylor does not teach or suggest the methods of independent claim 18 (and claims dependent therefrom, including claims 38, 39, 40, 42, 46, and 48) and new independent claim 51 (and claims dependent therefrom).

The deficiencies in Taylor are not cured by Ebenbichler and Nilsson. As discussed above in Section 4.2, Nilsson describes the production of murine monoclonal antibodies that bind to distinct neoantigenic epitopes on bound C3b and C3b(i). Ebenbichler describes a direct interaction between C1 complex and HIV-1 and suggests that the interaction results in the enhancement of HIV-1 infection. Neither Nilsson nor Ebenbichler teach, suggest or contemplate methods of inhibiting or suppressing viral replication in an animal comprising administering to the animal an anti-C3b(i) antibody, whether a monoclonal antibody immunospecific for C3b(i) or a bispecific antibody immunospecific for C3b(i) and an effector cell or antigen. Moreover, contrary to the Examiner's contention, one of skill in the art would not have been motivated to administer red blood cells franked with heteropolymers comprising of anti-CR1 antibodies conjugated to the anti-C3(D) antibody of Nilsson because of the teaching in Ebenbichler that activation of human complement by HIV-1 does not result in the lysis of HIV-1 and that the deposition of C3b facilitates HIV-1 infection of complement receptor-bearing cells (see the abstract of Ebenbichler). Accordingly, the rejection of claims 18, 24, 34, 38, 39, 40 and 48 under 35 U.S.C. § 103(a) as unpatentable over Taylor in view of Ebenbichler and Nilsson cannot stand and should be withdrawn.

4.8 Taylor In View of Ebenbichler, Nilsson, and Lenz Does Not Render Claims 18, 24, 33, 34, 36-40 and 48 Obvious

Claims 18, 24, 33, 34, 36-40 and 48 are rejected under 35 U.S.C. § 103(a) as unpatentable over Taylor, Ebenbichler and Nilsson as applied to claims 18, 24, 34, 38, 39 and

40, and further in view of Lenz. The Examiner contends that Taylor and Ebenbichler "render obvious the instant claims wherein the heteropolymer consists of anti-CR1 antibodies which bind to non-overlapping epitopes of CR1 conjugated to anti-C3(D) antibodies." The Examiner concedes that these references do not teach bispecific antibodies which bind CR1 and C3(D). However, the Examiner contends that Lenz teaches "bispecific antibodies which have two different antigen binding sites directed towards two different epitopes useful for the therapy of diseases", and provides as an example of a bispecific antibody one which has one antigen binding site directed towards a T-cell surface antigen and a second antigen binding site directed towards an antigenic determinant of a virus. The Examiner contends that "[i]t would have been prima facie obvious to one of skill in the art at the time the invention was made to substitute bi-specific antibodies which bind to both the CR1 receptor of a red blood cell and C3(D) on the target free retroviruses or cells infected with retrovirus in the method rendered obvious by the combination of Taylor ... and Ebenbichler." The Examiner contends that one of skill in the art would have been motivated to make such substitution because of the teaching in Lenz regarding the ease of making such bispecific antibodies relative to chemically conjugating two different antibodies and the high yield of bispecific antibodies obtained using the method in Lenz. For the reasons detailed below, the rejection cannot stand and should be withdrawn.

As discussed above in Section 4.1, Taylor does not teach or suggest the methods of independent claim 18 (and claims dependent therefrom, including claims 38, 39, 40, 42, 46, and 48) and new independent claim 51 (and claims dependent therefrom).

The deficiencies in Taylor are not cured by Ebenbichler, Nilsson and Lenz. As discussed above in Section 4.2, Nilsson describes the production of murine monoclonal antibodies that bind to distinct neoantigenic epitopes on bound C3b and C3b(i). Ebenbichler describes a direct interaction between C1 complex and HIV-1 and suggests that the interaction results in the enhancement of HIV-1 infection. Lenz describes methods for producing hetero-bispecific antibodies. Neither Ebenbichler, Nilsson nor Lenz teach, suggest or contemplate methods of inhibiting or suppressing viral replication in an animal comprising administering to the animal an anti-C3b(i) antibody, whether a monoclonal antibody immunospecific for C3b(i) or a bispecific antibody immunospecific for C3b(i) and an effector cell or antigen. Accordingly, the rejection of claims 18, 24, 33, 34, 36-40 and 48 under 35 U.S.C. § 103(a) as unpatentable over Taylor, Ebenbichler and Nilsson as applied to claims 18, 24, 34, 38, 39 and 40, and further in view of Lenz cannot stand and should be withdrawn.

4.9 The Cited References Do Not Render Claims 21, 33, 34, 36-40, 43, 44, 47, 49 and 50 Obvious

Claims 21, 33, 34, 36-40, 43, 44, 47, 49 and 50 are rejected under 35 U.S.C. § 103(a) as unpatentable over Fanger et al., EP 0 255 249 A2 (hereinafter "Fanger") as evidenced by Abbas et al., Cellular and Molecular Immunology, 1991, pp. 398-400 (hereinafter "Abbas") in view of Newman et al., 1985, J. Exp. Med. 161: 1414-1431 (hereinafter "Newman"), and Nilsson as evidenced by Vogel et al., 1997, Infection and Immunity 65: 4022-4029 (hereinafter "Vogel"). The Examiner contends that: (1) Fanger teaches " a method for eliminating target cells which include microorganisms such as bacteria and viruses comprising administering a bi-specific antibody which binds to the Fc receptors of effector cells", such as human leukocytes, IFN-gamma activated neutrophils, IFN-gamma activated natural killer cells and eosinophils; (2) Abbas provides evidence that CD64, CD32 and CD16, which are recited in claim 37, are Fc receptors; (3) Newman teaches "that *E. coli*, *S. pneumoniae*, *S. pyrogenes*, *S. aureus* and *H. influenza* all activate the alternative complement pathway and require phagocytosis for removal from the host"; (4) Nilsson teaches "monoclonal anti-C3d antibodies which bind exclusively to neoantigenic epitopes found in physiologically bound C3"; and (5) Vogel provides evidence that "physiologically bound C3b and Cbi is linked to the surface of encapsulated bacteria which comprises LPS". The Examiner contends that "[i]t would have been prima facie obvious at the time the invention was made to use the anti-C3(D) antibodies of Nilsson [sp] ... in the method of eliminating bacteria as taught by Fanger ...." The Examiner contends that one of skill in the art would have been motivated to use such antibodies because of the teaching in Newman regarding the deposition of C3b on the surface of *E. coli*, *S. pneumoniae*, *S. pyrogenes*, *S. aureus* and *H. influenza* and the teaching in Nilsson regarding anti-C3(D) antibodies. For the reasons below, the rejection cannot stand and should be withdrawn.

None of the cited references teach or suggest the claimed methods. Fanger describes anti-Fc receptor antibodies and bifunctional antibodies comprising at least one antigen binding region derived from an anti-Fc receptor and at least one antigen binding region specific for a target cell or antigen for use in the treatment of cancer, allergies and infectious and autoimmune diseases. Fanger does not teach, suggest or contemplate methods inhibiting or suppressing microbial replication in an animal comprising administering to the animal an anti-C3b(i) antibody, whether a monoclonal antibody immunospecific for C3b(i), as recited

in claim 34, or a bispecific antibody immunospecific for C3b(i) and an effector cell or antigen, as recited in claim 33.

The deficiencies in Fanger are not cured by Newman, Abbas, Nilsson and Vogel. Newman provides data regarding the amount of C3b, C3b(i) and C3d,g deposited on various particles and microorganisms. Abbas is merely a table which provides the names of complement receptors, their ligands, cell distribution, molecular weight and biological function. Nilsson describes the production of murine monoclonal antibodies that bind to distinct neoantigenic epitopes on bound C3b and C3b(i). Vogel describes the deposition of C3 and serum in isogenic capsule and lipooligosaccharide sialic acid mutants of serogroup B *Neisseria meningitidis*. Neither Newman, Abbas, Nilsson nor Vogel, alone or in combination, teach or suggest methods inhibiting or suppressing microbial replication in an animal comprising administering to the animal an anti-C3b(i) antibody, whether a monoclonal antibody immunospecific for C3b(i) or a bispecific antibody immunospecific for C3b(i) and an effector cell or antigen. Thus, neither Fanger, Newman, Abbas, Nilsson nor Vogel, alone or in combination, teach or suggest the methods recited in pending claims 21, 33, 34, 36-40, 43, 44, 47, 49 and 50, let alone provide a reasonable expectation of success. Accordingly, the rejection of claims 21, 33, 34, 36-40, 43, 44, 47, 49 and 50 are rejected under 35 U.S.C. § 103(a) as unpatentable over Fanger as evidenced by Abbas in view of Newman, and Nilsson as evidenced by Vogel cannot stand and should be withdrawn.

4.10 The Cited References Do Not Render Claims 21, 33, 34, 36-40, 43, 44, 47, 49 and 50 Obvious

Claims 21, 33, 34, 36-40, 43, 44, 47, 49 and 50 are rejected under 35 U.S.C. § 103(a) as unpatentable over Fanger, Newman, Nilsson and Vogel as applied to claims 21, 33, 34, 36-40, 43, 44, 47, 49 and 50, and in further view of Todd et al., 1996, Journal of Clinical Investigation 98: 1-2 (hereinafter "Todd"), Fang et al., 1998, Journal of Immunology 160: 5273-5279 (hereinafter "Fang"), Abbas and the abstract of Pulford et al., 1990, International Immunology 2: 973-980 (hereinafter "Pulford"). For the reasons set forth in Section 4.9, the Examiner contends that Fanger as evidenced by Abbas, Newman and Nilsson "render obvious the instant claims wherein the effector antigen to which the bispecific or heterospecific antibodies bind is CD16, CD32 and CD64." The Examiner concedes that the combination does not specifically teach the effector cell antigens of CR4 or CD89. However, the Examiner contends that: (1) Fang teaches that CR1 is expressed on the surface of

erythrocytes, macrophages, neutrophils, B-cells, follicular dendritic cells and a subset of T-cells, and that CR2 is expressed on the surface of follicular dendritic cells; (2) Todd teaches that CR3 is expressed on the surface of mononuclear phagocytes and natural killer cells; and (3) Abbas identifies CR4 as found on neutrophils and monocytes. The Examiner contends that "[i]t would have been prima facie obvious at the time the invention was made to use the method rendered obvious by the combination of Fanger ..., Newman ... and Neilsson [sp] ... to target leukocytes, such as macrophages, neutrophils or natural killer (NK) cells by means of bispecific antibodies or heteroantibodies which bind to CR1, CR2, CR3, CR4, or CR68." The Examiner contends that one of skill in the art would have been motivated to use such methods because of the teachings in Fang, Todd, Abbas or Pulford regarding the expression of such antigens on leukocytes and the suggestion by Fanger that the effector cells could be leukocytes. For the reasons below, the rejection cannot stand and should be withdrawn.

As discussed above in Section 4.9, neither Fanger, Abbas, Newman nor Nilsson, alone or in combination, teach or suggest the methods in pending claims 21, 33, 34, 36-40, 43, 44, 47, 49 and 50.

The deficiencies in Fanger, Abbas, Newman and Nilsson are not cured by Todd, Fang or Pulford. Todd is merely an editorial regarding CR3. Fang describes the requirement for CR1 and CR2 expression on follicular dendritic cells for generating a normal humoral immune response. Pulford describes the expression of CD68 on cells hemopoietic and non-hemopoietic cells. Neither Fang, Todd nor Pulford, alone or in combination, teach or suggest methods inhibiting or suppressing microbial replication in an animal comprising administering to the animal an anti-C3b(i) antibody, whether a monoclonal antibody immunospecific for C3b(i), as recited in claim 34, or a bispecific antibody immunospecific for C3b(i) and an effector cell or antigen, as recited in claim 33. Thus, neither Fanger, Newman, Abbas, Nilsson, Fang, Todd nor Pulford, alone or in combination, teach or suggest the methods recited in pending claims 21, 33, 34, 36-40, 43, 44, 47, 49 and 50, let alone provide a reasonable expectation of success. Accordingly, the rejection of claims 21, 33, 34, 36-40, 43, 44, 47, 49 and 50 under 35 U.S.C. § 103(a) as unpatentable over Fanger, Newman, Nilsson and Vogel as applied to claims 21, 33, 34, 36-40, 43, 44, 47, 49 and 50, and in further view of Todd, Fang and Pulford cannot stand and should be withdrawn.

4.11 The Cited References Do Not Render Claims 21, 24-37, 33, 34, 36-40, 43, 44, 47, 49 and 50 Obvious

Claims 21, 24-27, 33, 34, 36-40, 43, 44, 47, 49 and 50 are rejected under 35 U.S.C. § 103(a) as unpatentable over Fanger, Abbas, Newman, Nilsson and Vogel as applied to claims 21, 33, 34, 36-40, 43, 44, 47, 49 and 50, and further in view of Quie et al., 1981, Scand. J. Infect. Dis. Suppl. 31: 34-40 (hereinafter "Quie"). For the reasons described above, the Examiner contends that Fanger, Abbas, Newman, Nilsson and Vogel render obvious claims 21, 33, 34, 36-40, 43, 44, 47, 49 and 50, wherein the effector cell antigen to which the bispecific or heterospecific antibodies to CD16, CD32 and CD64. The Examiner concedes that these references do not teach the administration of IgG or IgM enriched plasma. However, the Examiner contends that Quie teaches "that IgG antibodies on the surface of microbes are efficient opsonins acting by attachment of the antibody Fc region to the Fc receptors on phagocytic cells and that IgM antibodies are efficient activators of complement on the surface of microbes and act indirectly as opsonins by fixing C3b which can then attach to C3b receptors on phagocytic cells." The Examiner contends that "[i]t would have been prima facie obvious at the time the claimed invention was made to further administer IgG enriched and IgM enriched plasma and C3b molecules in addition to the bispecific or heterospecific antibodies rendered obvious by the teachings of Fanger ... as evidenced by Abbas ..., Newman ... and Neilsson [sp] ...." For the reasons below, the rejection cannot stand and should be withdrawn.

As discussed above in Section 4.9, neither Fanger, Abbas, Newman, Nilsson nor Vogel render obvious, alone or in combination, teach or suggest the methods in pending claims 21, 33, 34, 36-40, 43, 44, 47, 49 and 50. The deficiencies of these references is not cured by Quie. Quie is a review article regarding humoral factors in the host defense against microbes. Quie does not teach or suggest methods inhibiting or suppressing microbial replication in an animal comprising administering to the animal an anti-C3b(i) antibody, whether a monoclonal antibody immunospecific for C3b(i) or a bispecific antibody immunospecific for C3b(i) and an effector cell or antigen, alone or in combination with IgG or IgM enriched plasma or one or more complement components. Accordingly, the rejection of claims 21, 24-27, 33, 34, 36-40, 43, 44, 47, 49 and 50 under 35 U.S.C. § 103(a) as unpatentable over Fanger, Abbas, Newman, Nilsson and Vogel as applied to claims 21, 33, 34, 36-40, 43, 44, 47, 49 and 50, and further in view of Quie cannot stand and should be withdrawn.

4.12 The Cited References Do Not Render Claims 21, 22, 32, 33, 34, 36-40, 43-45, 47, 49 and 50 Obvious

Claims 21, 22, 32, 33, 34, 36-40, 43-45, 47, 49 and 50 are rejected under 35 U.S.C. § 103(a) as unpatentable over Fanger as evidenced by Abbas, Newman, Nilsson, and Vogel as applied to claims 21, 33, 34, 36-40, 43, 44, 47, 49, 50, and further in view of Seelen et al., 1995, Immunology 84: 653-661 (hereinafter "Seelen"). For the reasons described above, the Examiner contends that Fanger, Abbas, Newman, Nilsson and Vogel render obvious claims 21, 33, 34, 36-40, 43, 44, 47, 49, 50 for the clearance of bacteria from a patient by means of bispecific or heterospecific antibodies that bind to C3b or C3b(i) and an effector cell antigen. The Examiner concedes that these references do not teach the treatment of sepsis or the administration of an antibody immunospecific for one or more microbial antigens. However, the Examiner contends that Seelen teaches: (i) the administration of a human anti-lipid A IgM antibody to treat patients with presumed gram-negative sepsis; (ii) "that the anti-lipid A antibody binds to rough and smooth gram negative bacteria and that binding to the 'rough' gram negative organism, S. minnesota, enhanced classical pathway complement fixation, deposition of C3bi on the bacterial surface and mediated binding to erythrocyte CR1 to monocytes"; and (iii) "that complement fixation, delivery to the reticulo-endothelial system or direct enhancement of opsonization contributes to the clearance of certain bacteria in the septic patient." The Examiner contends that "[i]t would have been prima facie obvious at the time the claimed invention was made to treat sepsis by the method rendered obvious in the combination of Fanger ... as evidenced by Abbas ... and Newman ... and Nilsson ... and Vogel in addition to the administration of an anti-lipid A antibody." The Examiner contends that one of skill in the art would have been motivated to treat sepsis in such a way because of the teaching in Seelen regarding the enhancement of C3 deposition by the anti-lipid A antibody, E5, and one would of skill in the art would want to increase the amount of Cb(i) on the surface of bacteria to more efficiently target the bispecific or heterospecific antibodies of Fanger. For the reasons below, this rejection cannot stand and should be withdrawn.

As discussed above, neither Fanger, Abbas, Newman, Nilsson nor Vogel, alone or in combination, teach or suggest methods inhibiting or suppressing microbial replication in an animal comprising administering to the animal an anti-C3b(i) antibody, whether a monoclonal antibody immunospecific for C3b(i) or a bispecific antibody immunospecific for C3b(i) and an effector cell or antigen, alone or in combination with an antibody

immunospecific for a microbial antigen. Further, neither Fanger, Abbas, Newman, Nilsson nor Vogel, alone or in combination, teach or suggest methods of treating septic shock in animal comprising administering to the animal an anti-C3b(i) antibody.

The deficiencies of Fanger, Abbas, Newman, Nilsson and Vogel are not cured by Seelen. Seelen describes possible mechanisms by which the anti-lipid A monoclonal antibody E5 may enhance bacterial clearance based upon interactions observed *in vitro* between the anti-lipid A monoclonal antibody E5 and particular gram-negative bacteria, complement, erythrocytes and monocytes. Seelen does not teach or suggest methods of inhibiting or suppressing microbial replication in an animal comprising administering to the animal an anti-C3b(i) antibody, whether a monoclonal antibody immunospecific for C3b(i) or a bispecific antibody immunospecific for C3b(i) and an effector cell or antigen, much less the administration of an anti-C3b(i) antibody in combination with an antibody immunospecific for a microbial antigen to inhibit or suppress microbial replication. Further, Seelen does not teach or suggest methods of treating sepsis in an animal comprising administering an anti-C3b(i) antibody. Accordingly, the rejection of claims 21, 22, 32, 33, 34, 36-40, 43-45, 47, 49 and 50 under 35 U.S.C. § 103(a) as unpatentable over Fanger as evidenced by Abbas, Newman, Nilsson, and Vogel as applied to claims 21, 33, 34, 36-40, 43, 44, 47, 49, 50, and further in view of Seelen cannot stand and should be withdrawn.

CONCLUSION

Applicants believe that the present claims meet all the requirements for patentability. Entry of the foregoing amendments and remarks into the file of the above-identified application is respectfully requested. Withdrawal of all rejections and reconsideration of the amended claims are requested.

If any issues remain, the Examiner is requested to telephone the undersigned at (212) 326-3630.

Respectfully submitted,

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Margaret B. Brivanlou (Reg. No.)

JONES DAY
222 East 41st Street
New York, New York 10017
(212) 326-3939